Comparative effectiveness of high-dose versus standard-dose influenza vaccines in US residents aged 65 years and older from 2012 to 2013 using Medicare data: a retrospective cohort analysis

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Summary

Background—A high-dose trivalent inactivated influenza vaccine was licensed in 2009 by the US Food and Drug Administration (FDA) on the basis of serological criteria. We sought to establish whether high-dose inactivated influenza vaccine was more effective for prevention of influenza-related visits and hospital admissions in US Medicare beneficiaries than was standard-dose inactivated influenza vaccine.

Methods—In this retrospective cohort study, we identified Medicare beneficiaries aged 65 years and older who received high-dose or standard-dose inactivated influenza vaccines from community pharmacies that offered both vaccines during the 2012–13 influenza season. Outcomes were defined with billing codes on Medicare claims. The primary outcome was probable influenza infection, defined by receipt of a rapid influenza test followed by dispensing of the neuraminidase inhibitor oseltamivir. The secondary outcome was a hospital or emergency department visit, listing a Medicare billing code for influenza. We estimated relative vaccine effectiveness by comparing outcome rates in Medicare beneficiaries during periods of high influenza circulation. Univariate and multivariate Poisson regression models were used for analyses.

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Findings—Between Aug 1, 2012 and Jan 31, 2013, we studied 929 730 recipients of high-dose vaccine and 1 615 545 recipients of standard-dose vaccine. Participants enrolled in each cohort were well balanced with respect to age and presence of underlying medical disorders. The high-dose vaccine (1·30 outcomes per 10 000 person-weeks) was 22% (95% CI 15–29) more effective than the standard-dose vaccine (1·01 outcomes per 10 000 person-weeks) for prevention of probable influenza infections (rapid influenza test followed by oseltamivir treatment) and 22% (95% CI 16–27%) more effective for prevention of influenza hospital admissions (0·86 outcomes per 10 000 person-weeks in the high-dose cohort *vs* 1·10 outcomes per 10 000 person-weeks in the standard-dose cohort).

Interpretation—Our retrospective cohort study in US Medicare beneficiaries shows that, in people 65 years of age and older, high-dose inactivated influenza vaccine was significantly more effective than standard-dose vaccine in prevention of influenza-related medical encounters. Additionally, the large population in our study enabled us to show, for the first time, a significant reduction in influenza-related hospital admissions in high-dose compared to standard-dose vaccine recipients, an outcome not shown in randomised studies. These results provide important new information to be considered by policy makers recommending influenza vaccinations for elderly people.

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Introduction

Elderly people are at an increased risk of severe influenza-related complications compared with young people.[1,2] People aged 65 years and older account for more than 90% of all influenza deaths.[3] Despite this serious public health burden, only one large randomised placebo-controlled trial of the efficacy of an inactivated influenza vaccine in elderly people has been done.[4–6] That study[6] showed an efficacy of 58% (95% CI 26–77) for the prevention of symptomatic clinical illness associated with laboratory-confirmed influenza illness in participants aged 60 years and older; in those aged 60–69 years, vaccine efficacy was 59% (20 to 79), whereas in participants aged 70 years and older, it was 57% (−36 to 87). Thus, most information about the effects of the influenza vaccine in people aged 65 years and older is based on observational studies. In these studies,[7–9] estimates of effective ness of standard-dose inactivated influenza vaccines in the prevention of serious influenza-associated outcomes in people aged 65 years and older have varied widely, suggesting moderate to no effectiveness. Identification of ways to improve the clinical effects of influenza vaccination to reduce influenza disease and its complications in people aged 65 years and older is a public health priority. Researchers have been exploring new vaccines that might increase effectiveness in elderly people.[10]

In December, 2009, the US Food and Drug Administration (FDA) licensed an injectable inactivated trivalent influenza vaccine (Fluzone High-Dose, Sanofi Pasteur, PA, USA), hereafter referred to as the high-dose vaccine. High-dose vaccines contain about four times more influenza haemagglutinin antigen than standard-dose influenza vaccines (60 μg *vs* 15 μg per strain).[11] The high-dose vaccine was approved by the FDA for use in individuals aged 65 years and older, according to accelerated approval regulations.[12] These regulations are applicable to products for treatment or prevention of serious illnesses that provide

meaningful therapeutic benefit compared with existing treatments. The data supporting effectiveness needed for licensure of high-dose vaccines came from immunogenicity studies showing that the high-dose vaccines elicited higher haemagglutination inhibition titres than standard-dose Fluzone in adults aged 65 years and older against influenza virus A strains H1N1 and H3N2, and non-inferior antibody titres for the B strain, included in the vaccine, compared with standard-dose Fluzone.[13] Results from a Sanofi -sponsored post-licensure randomised controlled trial[14] of high-dose versus standard-dose vaccine in about 30 000 participants aged 65 years and older showed superior efficacy of the high-dose vaccine for prevention of laboratory-confirmed influenza infections. However, despite the large number of participants enrolled, this study was not powered to characterise efficacy against serious influenza-related outcomes, including hospital admissions.

Additional data for the effectiveness of the high-dose vaccine are needed to obtain data for hospital admissions and other influenza-related outcomes of interest. To quantify the effectiveness of high-dose versus standard-dose vaccines against illness in the community setting and severe out comes in adults aged 65 years and older, we did a retrospective cohort study in US adults aged 65 years and older using Medicare fee-for-service databases. Thus, unlike the published clinical randomised control trial,[14] we were able to estimate relative vaccine effectiveness by age subgroups for serious influenza illnesses resulting in hospital admission. We hypothesised, on the basis of immunogenicity data available at the time of vaccine licensure,[13] that the high-dose vaccine would be more effective than the standard-dose vaccine at preventing influenza-associated outcomes in US Medicare beneficiaries.

Methods

Study design and participants

In this retrospective cohort analysis, we used influenza vaccination and infection rates from administrative files for the population on the US Medicare programme. See appendix for the full study protocol.

Our study's base population was drawn from fee-for-service Medicare beneficiaries aged 65 years and older who had a Healthcare Common Procedure Coding System (HCPCS) or a Current Procedural Terminology (CPT) code for a high-dose influenza vaccination (CPT of 90662) or standard-dose vaccination (CPT of 90655–90661 or 90724; HCPCS of G0008 or Q2035-Q2038) between Aug 1, 2012, and Jan 31, 2013. Each beneficiary was enrolled in Medicare parts A and B for at least 6 months before vaccination to detect comorbidities, and each remained in the study population while still enrolled and alive. Each beneficiary was also enrolled in Medicare part D from Aug 1, 2012, throughout the high influenza season. Beneficiaries diagnosed with influenza before vaccination or recorded as having received both a high-dose and standard-dose influenza vaccination between Aug 1, 2012, and May 31, 2013, were excluded from the study. Beneficiaries who received standard-dose or high-dose vaccine at a community pharmacy that vaccinated at least one other beneficiary with the alternative influenza vaccine in the 2 weeks preceding or following the index vaccination were eligible for inclusion in the study. This restriction was designed to ensure that each participant had equal access to both vaccinations and was sufficiently healthy to enter a community pharmacy and request influenza vaccination. We believe that the request for

vaccination at a community pharmacy implied a minimum amount of self-care ability in cohort members, which would decrease the bias associated with differences in frailty between recipients of each vaccine.[8] Additionally, this community pharmacy-based matching attempted to account for temporal and geographic factors possibly associated both with access to the high-dose vaccine and influenza disease exposure.

Procedures

For each beneficiary in the study, we linked Medicare enrolment and demographic data to claims from inpatient and community settings to track influenza vaccination trends, define outcomes, and establish population characteristics. We used the proportion of samples testing positive for influenza infection in samples submitted to laboratories collaborating with the National Respiratory and Enteric Virus Surveillance System (NREVSS).[15] This Centers for Disease Control and Prevention (CDC)-sponsored nationwide laboratory-based surveillance system monitors temporal and geographic patterns associated with the detection of influenza and other respiratory and enteric viruses. We used NREVSS data to define high, medium, and low influenza periods on the basis of previously published criteria.[16,17]

Outcomes

Our primary outcome was a probable episode of influenza-related illness defined by a community medical encounter with the provision of a rapid influenza diagnostic test coded with CPT 87804,[18] followed by a therapeutic dispensing of oseltamivir within a 2-day period (oseltamivir, 75 mg twice daily for 5 days).[19] Several outcomes attributed to one participant were included in the analysis because contraction of influenza more than once is possible during an influenza season. We did not include other influenza test types in our definition because delays in availability of test results would affect the prescription of influenza-specific antivirals by health-care providers.[20] The rapid influenza diagnostic test and oseltamivir treatment definition included only medical encounters that occurred in a community setting because Medicare does not code prescriptions dispensed in hospital inpatient or emergency department outpatient claims, and thus, such data were not available to the investigators. In the Centers for Medicare and Medicaid Services (CMS), community setting refers to outcomes observed in a non-institutional setting or outpatient non-emergency department setting.

Our secondary outcome was a hospital inpatient admission or emergency department visit diagnosis of influenza, defined by International Classification of Diseases, ninth revision, Clinical Modification (ICD-9-CM) codes 487.xx or 488.xx. Diagnosis codes specific to influenza suggest a health-care provider's assessment that the Medicare beneficiary has an influenza-associated illness, which might not be confirmed by influenza testing. We used the influenza-associated outcome to capture emergency department visits or hospital admissions with influenza-like illness because of the unavailability of antiviral prescription or laboratory testing data that can be used to define influenza infection in the community setting.

Statistical analysis

To assess the comparability of the high-dose and standard-dose vaccine cohorts, we examined differences between baseline characteristics across cohorts using standardised

mean differences, calculated as the difference in means or proportions of a variable divided by the pooled SD of the variable. A standardised mean difference of 0·1 or greater would suggest a substantial difference in means or proportions between groups.[21,22] The large numbers of enrolled participants means that small, clinically insignificant differences might have been statistically significant using standard p value cut-off points, such as p=0·05.

Outcome rates were calculated as the number of outcomes per person-time for both high-dose and standard-dose cohorts during the high-influenza period. Periods of influenza activity were classified as low, medium, or high based on CDC influenza virus surveillance data in the four US census regions. High periods of influenza activity included weeks when the proportion of respiratory samples that tested positive for influenza was at the 75th or greater percentile and low periods of influenza activity included the 55th percentile or lower from August, 2012, to August, 2013. We calculated the person-time denominator by summing the number of weeks that beneficiaries were enrolled for each region and period. We calculated the number of outcomes by week and region to establish the numerator.

Relative vaccine effectiveness (RVE) was estimated by the following equation: RVE=(1 − rate high-dose recipients/rate standard-dose recipients) × 100.

We accounted for potential confounders of the vaccine and outcome association by using multivariate Poisson regression models. The RVE estimates from the multivariate model were adjusted using the list of characteristics in table 1. All analyses were done using STATA version 13.

Role of the funding source

The US Food and Drug Administration made contributions to the design of the study, analysis of the data, interpretation of the results, and writing of the manuscript. The Assistant Secretary of Planning and Evaluation had no role in the design and conduct of the study, in the collection, analysis, and interpretation of the data, or in the preparation, review, or approval of the manuscript. NT had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The corresponding author was responsible for the final decision to submit for publication.

Results

Between Aug 1, 2012 and Jan 31, 2013, 12 509 108 Medicare beneficiaries aged 65 years and older received influenza vaccinations. Of these beneficiaries, 2437077 (19%) received high-dose inactivated influenza vaccine, whereas 10 072 031 (81%) received standard-dose influenza vaccine. From these groups, we identified a cohort of 2 545 275 individuals who were vaccinated at 24 501 pharmacies that offered both vaccines during the 2 week periods. Overall, 929 730 (7·4%) beneficiaries received the high-dose vaccine and 1 615 545 (13%) received a standard-dose vaccine. The two groups were similar in age and underlying medical disorders, although we identified some differences in regional composition of the cohorts (table 1). We compared the high-dose and standard-dose groups by the presence of each of the 189 medical disorder categories designated for Medicare risk adjustment.[24] No standardised mean difference in the proportions of beneficiaries with any of these disorders

was greater than 0·2. Table 1 shows results for disorder categories grouped into classifications associated with increased risk of serious complications of influenza infection, as defined by CDC's Advisory Committee on Immunization Practices.[21,22] Health disorders remained well balanced when high-dose versus standard-dose vaccine recipients were stratified into three age groups (65–74 years, 75–84 years, 85 years and older), although differences by region persisted (data not shown). The correlation coefficient between influenza hospital admission claims and community claims for rapid influenza diagnostic tests followed by the dispensing of oseltamivir was 0·97.

During the high influenza season, the rapid influenza diagnostic test followed by oseltamivir treatment outcome occurred more frequently in the standard-dose recipients (1·30 outcomes per 10 000 person-weeks) than in the high-dose recipients (1·01 outcomes per 10 000 person-weeks), corresponding to a risk difference of 0·29 (95% CI 0·19–0·38; figure 1). We observed differences in outcomes between treatment groups in each age group (figure 2). Community outcomes were rare during periods of low influenza circulation, whereas we identified small differences in outcome during medium periods, and differences were most apparent during periods of high influenza circulation. Repeat outcomes were rare; we noted seven repeat community-based outcomes and no repeat influenza hospital admissions.

Receipt of the high-dose vaccine was correlated with a reduction in influenza inpatient hospital admissions and emergency department visits (0·86 outcomes per 10 000 person-weeks) relative to receipt of the standard dose vaccine (1·10 outcomes per 10 000 person-weeks; figure 2), corresponding to a risk difference of 0·24 (95% CI 0·17–0·30). The hospital admissions and emergency department outcome occurred more frequently in those aged 85 years and older than in younger age groups (figure 2).

In univariate analyses, the high-dose vaccine was more effective than the standard-dose vaccine in Medicare beneficiaries aged 65–74 years, 75–84 years, and 85 years and older (figure 3). For our primary outcome of the rapid influenza diagnostic tests followed by oseltamivir in the community setting, we identified a 22% (95% CI 15–29) reduction in rapid influenza diagnostic test followed by oseltamivir in the community setting high-dose vaccine group (1·30 outcomes per 10 000 person-weeks) compared with the standard-dose vaccine group (1·01 outcomes per 10 000 person-weeks) in all beneficiaries, and a 36% (95% CI 13–54) reduction in those aged 85 years and older (0·62 outcomes per 10 000 person-weeks in the high-dose cohort compared with 0·98 outcomes per 10 000 person-weeks in the standard-dose cohort). The difference in relative vaccine effective-ness between the overall and the 85 years and older groups was not statistically significant (p=0·11 for a two-sided test). In terms of the prevention of hospital admission and emergency department visits, relative vaccine effectiveness in all beneficiaries was 22% (0·86 outcomes per 10 000 person-weeks in the high-dose cohort compared with 1·10 outcomes per 10,000 person weeks in the standard-dose cohort; 95% CI 16–27). The high-dose vaccine was more effective than the standard-dose vaccine for prevention of influenza-related outcomes in both hospital and emergency department and community settings for all age groups (figure 3). All effect estimates were consistent, whether derived from univariate or multivariate Poisson model regressions (table 2).

Discussion

During the 2012–13 influenza season, we identified that the high-dose influenza vaccine was 22% (95% CI 15–29) more effective at preventing influenza-associated illness treated in the community setting than standard-dose vaccine in a subset of US Medicare beneficiaries aged 65 years and older (panel). We identified a similar effect for influenza-associated hospital admissions and emergency department visits in this group. Our results are similar to the relative efficacy estimates reported in a completed, two-season, randomised controlled study of high-dose versus standard-dose Fluzone done by the manufacturer in more than 30 000 older adults.[14] In that study, the high-dose vaccine was 24% (95% CI 19–37) more effective at preventing reverse transcription PCR-confirmed influenza infections in adults aged 65 years and older than standard-dose vaccine.[13] In the community setting, the estimated relative effectiveness of the high-dose vaccine was higher in Medicare beneficiaries aged 85 years and older than in younger age groups, but this difference was not statistically significant.

Panel

Research in context

Systematic review

Only a few studies of the efficacy, and none of the effectiveness, of the high-dose influenza vaccine have been published.[13,14] We did a systematic title-match PubMed review using the search terms "influenza vaccine effectiveness high dose" and "influenza vaccine efficacy high dose." Only one of the three studies[14] identified was relevant for comparison with the current study: Sanofi Pasteur's double-blind, randomised, active-controlled comparative effectiveness trial that included more than 31 000 participants.[14] That study reported that the high-dose vaccine was 24% (95% CI 19–37) more effective at preventing reverse transcription PCR-confirmed influenza infections in adults aged 65 years and older than the standard-dose vaccine.

Interpretation

Our study identified that the high-dose vaccine was more effective than the standard-dose vaccine to prevent influenza illness treated in both community and inpatient settings. Our frequency matching by community pharmacy resulted in a strong balance in observable potential confounders between the two groups. We had more than 2·5 million study participants after applying cohort restrictions, allowing us to undertake analyses by age into influenza hospital admissions, of particular interest to beneficiaries, providers, regulators, and public health officials. Therefore, our finding of a significantly higher relative effectiveness with the high-dose vaccine against influenza-associated illnesses, confirmed for all age groups analysed, adds important new information. In future studies, these methods might also be used to estimate the possible mortality benefits of newer influenza vaccines. Moreover, our successful use of new methods both for matching and for defining outcomes, in a system that provides coverage for almost all older US adults, opens the door for studies to estimate effectiveness against serious outcomes in specific risk groups in near-real time, for pandemic and other new vaccines.

A strength of our study is that its population base includes patients identified through Medicare claims data, or about 98% of the US population aged 65 years and older.[25] Medicare provides inpatient, emergency department, and community fee-for-service care for 37 million beneficiaries and prescription coverage for 23 million of these beneficiaries as of January, 2014.[26] In view of the representativeness of these data, we believe that CMS data sources have great potential for use in observational studies in elderly people. Another strength of this study is the unusual comparability of beneficiaries in the high-dose and standard-dose vaccine groups, which underline the potential usefulness of studying Medicare beneficiaries who are vaccinated in a community pharmacy setting.

This study has several limitations. One potential limitation of the use of Medicare data is the unknown reliability of the ICD-9-CM codes used for the diagnosis of influenza in the community setting. Therefore, we developed an alternative definition for an influenza-related event, consisting of an influenza test followed by the prescription of oseltamivir (an antiviral used exclusively for influenza). Our use of only rapid influenza diagnostic test might have marginally decreased study power during the study period because only 75% of all influenza tests ordered were rapid influenza diagnostic tests. Our results are probably not generalisable to the whole US elderly population because we restricted the analysis to a subset of patients who received influenza vaccination in a community pharmacy setting. Another potential limitation in the use of our definition is that providers might find specific influenza test results most helpful at the beginning and end of influenza seasons and rely on symptoms and history to identify people with influenza infections during the peak of each season. Thus, we might have missed people with influenza, although we do not believe that the likelihood of influenza testing depended on whether a person received the high-dose or standard-dose vaccine.

Influenza-related hospital admissions might also be associated with secondary bacterial infections and with respiratory syncytial virus or other respiratory viral co-infections. Lower respiratory tract infections associated with these respiratory pathogens are difficult to distinguish and assigning a primary pathogen in patients with several infections is also difficult.[27–29] However, the near-perfect correlation between influenza hospital admission claims and community claims for rapid influenza diagnostic test followed by the dispensing of oseltamivir suggests that our hospital admission outcome during periods of high influenza circulation was specific for influenza-related events.

Another limitation of this study is that we did not have access to laboratory results and, therefore, could not define laboratory-confirmed outcomes. Instead, we developed what we believe is a specific outcome that combined a physician's order for a rapid influenza diagnostic test followed by the dispensing of an influenza-specific antiviral within the 2 days after the medical encounter. Because rapid influenza diagnostic test can provide a health-care provider with a result within 15 min after sample collection,[30] the test results can reasonably be expected to guide the decision to prescribe oseltamivir. Therefore, the combination of the rapid influenza diagnostic test and antivirals probably provides greater specificity than a physician diagnosis of influenza or a prescription of antivirals alone.[31,32]

As with all observational vaccine studies, vaccination was not randomly assigned and unmeasured confounders might bias our estimates of the relative effectiveness of high-dose vaccine.[33] However, restriction of the analysis to individuals who were vaccinated at a community pharmacy that offered both vaccines within a 2 week period seems to have yielded well balanced vaccine groups—at least in terms of a comparison of characteristics available and frequently used in pharma coepidemiology studies (eg, the 189 medical disorder categories considered).[34] The balance we achieved was probably improved by the fact that Medicare beneficiaries do not pay for influenza vaccination in community pharmacy settings, and thus, people were not dissuaded from receiving the more expensive high-dose vaccine. Although the restrictions we used decreased the study sample size, we still had large numbers of participants in both cohorts (about 930 000 high-dose and 1·6 million standard-dose recipients), and were able to do analyses by age group and also for a serious outcome: influenza hospital admissions.

We plan to do similar analyses in upcoming influenza seasons and to do medical record reviews in an attempt to further validate the influenza-related outcomes for a subset of beneficiaries. Our ability to detect and statistically confirm differences in relative effectiveness would be expected to vary with the severity of influenza seasons and with the match between the vaccine and circulating influenza strains. Relative vaccine effectiveness also might vary by influenza virus type and subtype, including new pandemic viruses. Because Medicare provides medical insurance coverage for almost all US adults aged 65 years and older, estimation of vaccine effectiveness for serious rare outcomes in specific risk groups is possible. Such assessments are usually not possible in randomised studies of comparative treatment or prevention modalities, even when tens of thousands of participants are randomly assigned in large, expensive studies. We plan to investigate the effectiveness of other vaccines administered to Medicare beneficiaries, and to do these assessments in near-real time[35] (eg, within 3 months of an event), as done for other FDA-CMS studies.[36–38]

Acknowledgments

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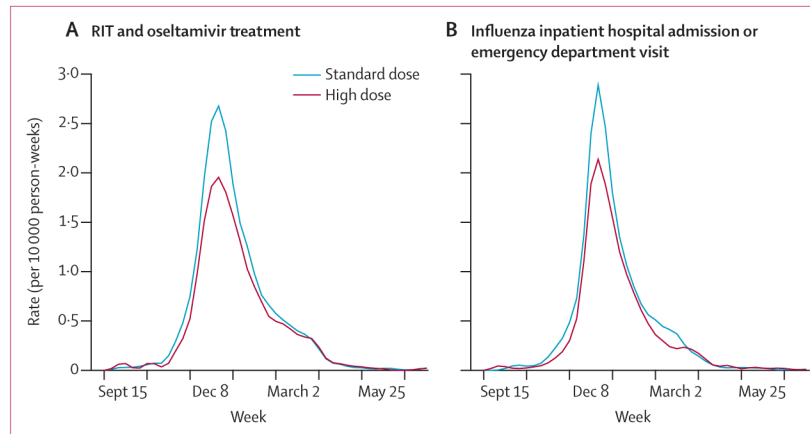
Figure 1. Influenza outcome rates by vaccine type during the 2012–13 influenza season
Each plot displays the rate of influenza per 10 000 person-weeks. Data was smoothed using a weighted average, placing a weight of 0·5 on the current week and a weight of 0·25 on the previous and following weeks. (A) Rapid influenza test followed by treatment with oseltamivir. (B) Inpatient hospital admissions or emergency department visits with an influenza International Classification of Diseases, ninth revision, Clinical Modification code. RIT=rapid influenza diagnostic test.
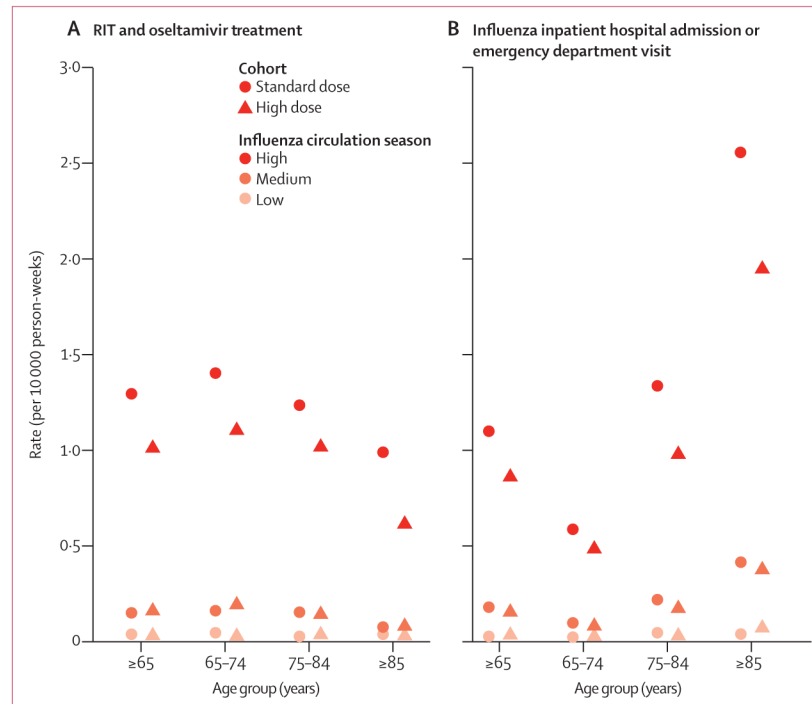
Figure 2. Influenza outcome rates in the 2012–13 influenza season
Each plot displays the rate of influenza per 10 000 person-weeks. (A) Community setting medical encounters including a rapid influenza test followed by treatment with oseltamivir. (B) Inpatient hospital admissions or emergency department visits with an influenza International Classification of Diseases, ninth revision, Clinical Modification code. Both graphs show the rates for the entire cohort (=65 years) and for the cohort stratified into three age groups (65–74 years, 75–84 years, and =85 years). The rates are shown for three periods during the season—high, medium, and low circulation. RIT=rapid influenza diagnostic test.
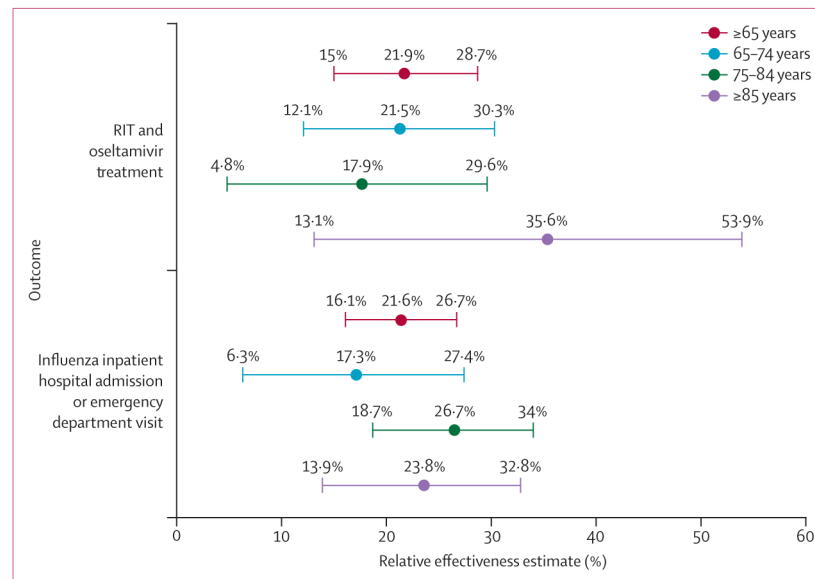
Figure 3. Relative vaccine effectiveness for different outcomes during the 2012–13 high influenza season

Shown are relative effectiveness and 95% CIs for two influenza outcomes. The top outcome is the measure of community medical encounters including a rapid influenza test followed by treatment with oseltamivir, and the bottom outcome is the measure of inpatient hospital admissions or emergency department visits with an International Classification of Diseases, ninth revision, Clinical Modification influenza code. For each outcome, we reported relative effectiveness for the entire cohort and for the cohort stratified into three age groups (65–74 years, 75–84 years, and =85 years). RIT=rapid influenza diagnostic test.

Table 1

Baseline characteristics of high-dose and standard-dose cohorts from 24 501 matched pharmacies

	High-dose cohort (n=929730)	Standard-dose cohort (n=1 615 545)	Standardised mean difference
Sex			
Female participants	538 380 (57·91%)	959 072 (59·37%)	0·03
Male participants	391 350 (42·09%)	656 473 (40·63%)	0·03
Race			
White	867 552 (93·31%)	1 512 633 (93·63%)	0·01
Black	25 463 (2·74%)	41 714 (2·58%)	0·01
Other race/unknown	16 235 (1·75%)	27 571 (1·71%)	<0·01
Asian	12 973 (1·40%)	21 178 (1·31%)	0·01
Hispanic	6112 (0·66%)	10 328 (0·64%)	<0·01
Native North American	1395 (0·15%)	2121 (0·13%)	0·01
Dual enrolled	45 186 (4·86%)	79 750 (4·94%)	<0·01
Age (years)	75·74 (7·19)	75·35 (7·27)	0·05
65–74	461 260 (49·61%)	841 789 (52·11%)	0·05
75–85	340 728 (36·65%)	561 385 (34·75%)	0·04
85 and older	127 742 (13·74%)	212 371 (13·15%)	0·02
Region			
Region 1: CT, ME, MA, NH, RI, VT	38 557 (4·15%)	101 886 (6·31%)	0·09
Region 2: NJ, NY, PR, VI	53 732 (5·78%)	128 825 (7·97%)	0·09
Region 3: DE, DC, MD, PA, VA, WV	90 367 (9·72%)	132 085 (8·18%)	0·05
Region 4: AL, FL, GA, KY, MS, NC, SC, TN	250 165 (26·91%)	381 632 (23·62%)	0·08
Region 5: IL, IN, MI, MN, OH, WI	117 795 (12·67%)	297 026 (18·39%)	0·16 [*]
Region 6: AR, LA, NM, OK, TX	103 532 (11·14%)	184 301 (11·41%)	0·01
Region 7: IA, KS, MO, NE	31 048 (3·34%)	80 014 (4·95%)	0·08
Region 8: CO, MT, ND, SD, UT, WY	44 257 (4·76%)	48 346 (2·99%)	0·09
Region 9: AZ, CA, HI, NV, AS, FS, GU, PU	137 678 (14·81%)	196 023 (12·13%)	0·08
Region 10: AK, ID, OR, WA	62 347 (6·71%)	65 056 (4·03%)	0·12 [*]
Other	252 (0·03%)	351 (0·02%)	<0·01
At least one high-risk disorder	560 929 (60·33%)	958 625 (59·34%)	0·02
Asthma	35 276 (3·79%)	59 557 (3·69%)	0·01
Blood disorders	96 553 (10·39%)	162 313 (10·05%)	0·01
Chronic lung disease	128 606 (13·83%)	214 689 (13·29%)	0·02
Diabetes [†]	186 269 (20·03%)	322 258 (19·95%)	<0·01

	High-dose cohort (n=929730)	Standard-dose cohort (n=1 615 545)	Standardised mean difference
Heart disease	302 605 (32·55)	508 973 (31·50%)	0·02
Kidney disorders	60 564 (6·51%)	100 047 (6·19%)	0·01
Liver disorders	16 418 (1·77%)	27 932 (1·73%)	<0·01
Neurological or neurodevelopmental conditions	99 777 (10·73%)	169 533 (10·49%)	0·01
Weakened immune system‡	106 803 (11·49%)	181 003 (11·20%)	0·01

Data are n (%) or mean (SD), unless otherwise specified.

[*]Common characteristics between the high-dose and standard-dose cohorts with a standard mean difference of more than or equal to 0·10, suggesting a substantial difference in proportions between groups.

[†]Diabetes was defined using the International Classification of Diseases, ninth revision, Clinical Modification and Healthcare Common Procedure codes.[23]

[‡]Weakened immune system was defined using the following Medicare condition categories: HIV/AIDS; metastatic cancer and acute leukaemia; lung or upper digestive or other severe cancer; lymphatic, head, neck, brain, or major cancer; breast, prostate, colorectal, or other cancer; and disorders of immunity

Table 2

Comparison of relative vaccine effectiveness between calculated rate ratio and adjusted and unadjusted Poisson models for the 2012–13 high influenza season

	RIT and oseltamivir treatment		Influenza inpatient hospital admissions or emergency department visit	
	Rate ratio	RVE (95% CI)	Rate ratio	RVE (95% CI)
Calculated rate ratio	0·781	21·9% (15·0–28·7)	0·784	21·6% (16·1–26·7)
Univariate Poisson model	0·782	21·8% (14·8–28·2)	0·783	21·7% (16·2–26·8)
Multivariate Poisson model	0·774	22·6% (15·7–29·0)	0·794	20·6% (14·9–24·8)

RIT=rapid influenza diagnostic test. RVE=relative vaccine effectiveness.